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A cross-sectional, multi-centric, epidemiological study of diabetic neuropathy and associated co-morbidities in type 2 diabetic patients in India

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ABSTRACT

Diabetic neuropathy (DN), one of the most common complications affects nerves in T2DM patients. This study was aimed to understand the clinical presentation of DN; types of neuropathies; associated co-morbidities, risk factors, treatment patterns etc. A single-visit, cross-sectional, multi-centric, epidemiological study conducted at 363 centres. Data collection included demographics, lifestyle habits, medical history, concomitant medications, laboratory investigations and treatment regimens in DN. A total of 7172 patients enrolled with mean age of 52.8 years. The median duration of T2DM was 6 years and neuropathy was about 2 years. The prevalence rates of painful and painless DN were 49.1% and 50.9%. The most common types of neuropathies reported were acute (32.3%) and chronic (31.4%) sensory neuropathy and reported symptoms were numbness (30.7%), paresthesia (29.2%), and burning sensation (28.0%). Majority of the patients had uncontrolled glucose parameters i.e FBG: 90.1%, PPG: 90.5%, HBA1c: 69.8% and uncontrolled lipid profile i.e LDL: 65.5% and TG: 61%. Almost 2/3rd (61.3%) were treated with metformin as monotherapy or in combination. More than half (52.3%) received mecobalamin for DN treatment. Higher proportions of patients with painful neuropathy were prescribed pregabalin as compared to painless (32.18% vs 19.79%). Diabetic neuropathy is painless in almost half of the Indian patients. Acute sensory neuropathy occurs in most of the patients. Onset of diabetic neuropathy could be much earlier than expected and hence, routine screening is recommended. Metformin and Mecobalamin are commonly prescribed for the treatment of diabetes and DN. Pregabalin is a preferred treatment option for painful DN.

Keywords: Type 2 Diabetes Mellitus (T2DM), Diabetic neuropathy (DN), Metformin, Mecobalamin, Pregabalin

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INTRODUCTION

Type 2 diabetes mellitus, is a chronic metabolic disorder characterized by hyperglycemia. In 2035, people with diabetes are estimated to increase by 55% globally, with majority of cases reported in developing countries. In India, 65.1 million people were diagnosed with diabetes in 2013.[1] The injurious effects of hyperglycemia can be classified into macrovascular (coronary artery disease, peripheral arterial disease and stroke) and microvascular complications (diabetic nephropathy, neuropathy and retinopathy). Longer duration of diabetes, poor glycemic and blood pressure control, dyslipidemia, smoking, and age at onset are some of the known risk factors for development of diabetic complications.[2] The Indian data from the multi-national A1chieve study revealed neuropathy (24.6%) as the most common complication followed by cardiovascular (23.6%), renal (21.1%), and eye (16.5%) complications.[3] Approximately, 20% of diabetic patients develop clinically significant neuropathy within 10 years of diabetes onset; and after 10 to 15 years, this proportion can increase to 50%.[4]

Diabetic neuropathy can be classified as peripheral, autonomic, proximal, focal and multifocal or mixed. It can exist with or without neuropathic pain. About 60 to 70% of people with diabetes have some neuropathy and about 11% complain of pain[5,6] Peripheral neuropathy is the most common neuropathy in diabetes mellitus. Acute sensorimotor neuropathy and chronic sensorimotor distal polyneuropathy are the most common types of peripheral neuropathy.[7] Injury to the nerves resulting from hyperglycemia may be related to mechanisms such as polyol accumulation, formation of advanced glycated end products and oxidative stress. More than 80% amputations occur after foot ulceration or injury resulting from diabetic neuropathy.[8,]

For prevention and treatment of neuropathy, the primary goal of therapy is optimum glucose control through diet, exercise, oral hypoglycemic agents and insulin. However, in a review article, the author Vinik highlights that though glycemic control is important, may not always prove useful in treating neuropathy. Development of neuropathy can be delayed significantly by maintaining glycemic levels to as near normal; however, early diagnosis and prompt treatment regimen for neuropathy should consider targeting the underlying pathogenesis.[9]

Currently, limited data exists to define characteristics of diabetic neuropathy in Indian diabetic population with or without neuropathic pain. The Indian subcontinent is termed as "the diabetes capital of the world"[10],[11]with prediction to have the highest prevalence of diabetes by 2030; the burden of diabetic neuropathy is bound to rise tremendously Diabetic neuropathy has a considerable negative impact on quality of life with a significantly worse trajectory of quality of life outcomes over time and increased long-term healthcare burden.

Thus, it is crucial that more studies are conducted to gain insight into the management of diabetic neuropathy in Indian population. This cross-sectional study was planned to understand the clinical presentation of diabetic neuropathy; types of neuropathy; associated co-morbidities and risk factors; and treatment patterns for diabetes and diabetic neuropathy in India.

Methodology

This was a single-visit, cross-sectional, multi-centric, epidemiological study conducted at 363 selected centres across four zones in India (Figure 1). It was conducted in compliance with the Declaration of Helsinki, International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) guidelines and other relevant regulatory guidelines. All the study documents were approved by the relevant Ethics Committees. All participants signed the participant authorization form as a documentation of voluntary participation in the study.

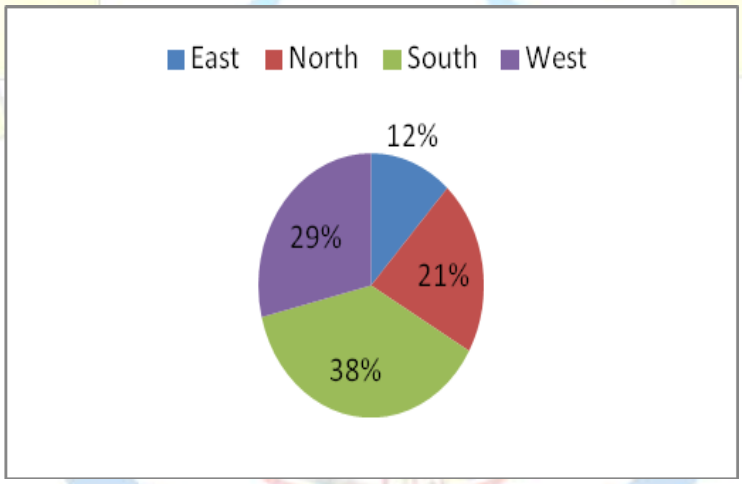

Figure 1: Distribution of study sites across different zones of India

Indian diabetic patients aged 18 to 65 years, diagnosed with diabetic neuropathy of any duration on treatment and visiting physician for a routine health check-up were included. Patients with any other neurological disorder that could mimic symptoms of neuropathy; pregnant or lactating women and those with significant pain, were excluded.

Study related information was recorded on the case report forms upon enrolment. Following data was collected: demography, lifestyle parameters (smoking status and alcohol consumption) and medical history (duration and treatment of diabetes and diabetic neuropathy, symptoms of diabetic neuropathy, type of diabetic neuropathy, concomitant medications and co-morbid conditions with duration). If available, data related to medical examinations (blood pressure, body mass index [BMI], and waist to hip ratio), and laboratory investigations (fasting plasma glucose [FPG], postprandial plasma glucose [PPG], glycosylated hemoglobin [HbA1c], low density lipoprotein cholesterol [LDL-C], high density

lipoprotein cholesterol [HDL-C], triglycerides, total cholesterol and vitamin D) was also collected.

Statistical analysis

No formal sample size calculation was done since this was a cross-sectional study. A total of 9460 patients were planned to be enrolled initially. All the enrolled patients constituted the analysis population. All statistical analyses were generated using Statistical Analysis System® Version 9.3 software for Windows. The continuous variables were summarized descriptively using number (n), mean and standard deviation (SD) or using median and range, while categorical data were presented using frequencies and percentages.

RESULTS AND DISCUSSION

A total of 7172 type 2 diabetic patients with diabetic neuropathy, visiting the selected study clinic for their routine check-up were screened and enrolled between January 2014 and November 2014. It was a pan India study; the southern zone had the highest number of selected centers and eastern zone had the least representation in the study conduct (Figure 1).

The mean (SD) age of the patients was 52.8 (± 8.04) years; majority being males (58%). The mean (SD) BMI and waist to hip ratio were 25.7 (± 3.88) kg/m^2 and 0.9 (± 0.18) respectively. A total of 709 of 6909 patients (9.9%) were smokers (455 [64.2%] smoked regularly) and 584 of 6905 (8.1%) were alcohol consumers (210 [36%] consumed alcohol regularly). The mean duration of smoking and alcohol consumption was approximately 13 years

The median duration of type 2 diabetes was 6 years (range 0.1 to 35 years) and diabetic neuropathy was about 2 years (range 0.1 to 30 years). The prevalence rates of painful and painless diabetic neuropathy were 49.1% and 50.9%, respectively. The most common types of neuropathies were acute sensory neuropathy (32.3%), chronic sensorimotor neuropathy (31.4%) and autonomic neuropathy (10.4%). The most frequently reported symptoms of diabetic neuropathy were numbness (30.7%), paraesthesia (29.2%), burning sensation (28.0%), and pain in extremity (17%). Data regarding other types of neuropathies and symptoms of neuropathy presented in less than 10% of overall population is not included. The distribution of patients for all analyzed variables between those with painful and painless neuropathy was numerically similar and hence, the data has not been presented separately. The characteristics of diabetes and diabetic neuropathy are presented in Table 1.

Table 1: Disease characteristics of patients

Characteristics	Value
Duration (years) of diabetes, median (range)	6.00 (0.1:35)
Duration (years) of diabetic neuropathy, median (range)	2.00 (0.1:30)
Type of neuropathy, n(%)	
Painful	3518 (49.1)

Painless	3654 (50.9)
Classification of neuropathy, n(%)*	
Acute sensory	2319 (32.3)
Chronic sensorimotor	2250 (31.4)
Autonomic neuropathy	779 (10.9)
Chronic inflammatory demyelinating polyneuropathy	708 (9.9)
Generalized symmetric polyneuropathy	428 (6.0)
Symptoms of neuropathy, n(%)	
Numbness	2205 (30.7)
Paraesthesia	2095 (29.2)
Burning sensation	2006 (28.0)
Pain in extremity	1216 (17.0)
Weakness	544 (7.6)
Sensory Loss	429 (6.0)
Peripheral swelling	408 (5.7)
Pain	298 (4.2)
Others	787 (10.97)

***** Types of neuropathy presented in less than 5% of patients are not included in the table.

The clinical characteristics of the patients are presented in Table 2. Higher proportion of the patients had uncontrolled levels of FPG (90.1%), PPG (90.5%), HbA1c (69.8%), LDL-C (65.5%) and triglycerides (61%).

Table 2: Clinical characteristics of patients

Characteristics	**Overall** N (mean ± SD)	**Patients with controlled parameters** n (%)	**Patients with uncontrolled parameters** n (%)
Systolic blood pressure (mmHg)	7172 (137.4 ± 18.73)	-	-
Diastolic blood pressure (mmHg)	7172 (85.1 ± 8.79)	-	-
Vitamin D (ng/mL)	7172 (18.3 ±8.71)	-	-
FPG (mg/dL)[a]	5193 (138.89 ± 36.30)	514 (9.9%)	4679 (90.1%)
PPG (mg/dL)[b]	5168 (204.23 ± 56.32)	490 (9.5%)	4678 (90.5%)
HbA1c (%)[c]	4308 (7.89 ± 1.33)	1299 (30.1%)	3009 (69.8%)
LDL-C (mg/dL)[a]	2196 (120.3 ± 36.19)	757 (34.5%)	1439 (65.5%)
HDL-C (mg/dL)[d]	2190 (43.0 ± 12.71)	1385 (63.2%)	805 (36.76%)
Triglycerides (mg/dL)[e]	2179 (173.9 ± 60.31)	849 (39%)	1330 (61%)
Total cholesterol (mg/dL)	2061 (197.0 ± 46.31)	1204 (58.4%)	857 (41.5%)

[a] >100 mg/dL; [b]>140 mg/dL; [c]> 7%; [d] >40 mg/dL; [e] >150 mg/dL were considered as uncontrolled laboratory value.

FPG: Fasting plasma glucose; PPG: Post-Prandial plasma glucose; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol

FPG > 100 mg/dL; PPG > 140 mg/dL; HbA1c > 7%; LDL-C > 100 mg/dL; and triglycerides > 150 mg/dL were considered as uncontrolled values for laboratory/lipid parameter.

Figure 2 represents the co-morbid conditions in patients with painful and painless diabetic neuropathy. The most common co-morbid condition reported was hypertension (1140; 15.9%) with the mean (SD) duration of 5.57 (4.10) years. The other co-morbidities reported

in up to 5% of the study population were nephropathy (2.5%), hypothyroidism (2.1%), vitamin D deficiency (2.1%), retinopathy (1.7%), and hyperthyroidism (0.7%). The mean (SD) duration of nephropathy, hypothyroidism, vitamin D deficiency, retinopathy and hyperthyroidism were, 2.60 (2.59), 6.43 (6.21), 1.67 (1.49), 2.73 (2.50) and 3.97 (4.15) years, respectively.

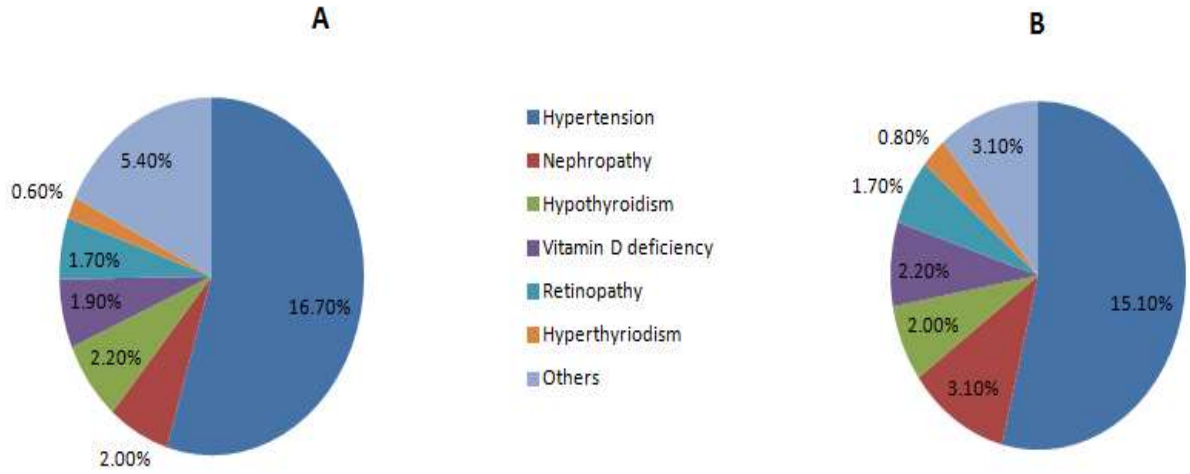

Figure 2: Co-morbid conditions in patients with painful (A) and painless (B) diabetic neuropathy

Data on concomitant medications were available for 1400 (19.5%) patients only. Of these 1400 patients, anti-hypertensive drugs including agents acting on the rennin-angiotensin system, calcium channel blockers, beta blockers and diuretics (81.4%) were the most common concomitant medication, followed by lipid modifying agents (22.4%). Other concomitant medications were prescribed in less than 10% of the study population.

A total of 7142 (99.6%) patients were on antidiabetic medications. The most common antidiabetic medication was metformin (61.3%) followed by glimepiride (46.2%), prescribed either as a monotherapy or as a combination. Insulin and its derivatives were prescribed in approximately 11% of total study population. The summary of treatment for diabetes is described in Table 3.

Based on the neuropathy symptoms, mecobalamin (52.30%) and pregabalin (25.9%) were commonly prescribed for treatment of diabetic neuropathy. Patients with painful neuropathy were frequently prescribed pregabalin (32.18%) as compared to those with painless neuropathy (19.79%). The mean (SD) duration of diabetic treatment was 3.80 (3.37) years and that of diabetic neuropathy treatment was 1.78 (6.12) years. The summary of treatment for diabetic neuropathy is described in Table 3.

Table 3: Summary of treatment for diabetes and diabetic neuropathy

Category	Overall (N=7172)*
Metformin	4377 (61.02)
Glimepiride	3301 (46.02)
Insulin and its derivatives	767 (10.64)
Gliclazide	599 (8.35)
Voglibose	481 (6.7)
Vildagliptin	362 (5.05)
Drugs used in the treatment of neuropathy	
Mecobalamin	3751 (52.30)
Pregabalin	1855 (25.86)
Folic acid, mecobalamin, pyridoxine hydrochloride, thioctic Acid	804 (11.21)
Folic Acid	736 (10.26)
Thioctic Acid	646 (9.01)

* Percentages were calculated taking respective column header count as denominator.
Anti diabetic drugs used in less than 5% of total population and drugs used in the treatment of neuropathy for less than 10 % of patients are not presented in table.

DISCUSSION

Diabetic neuropathy is one of the common complications of diabetes which is difficult to diagnose, control or reverse. It usually develops within 5-10 years of duration of diabetes. Vibration perception threshold and thermal test are effective in early diagnosis of diabetic neuropathy. Though hyperglycemia is majorly responsible for neuropathy, increased polyol pathway flux with accumulation of sugar alcohols, accumulation of advanced glycation end-products, oxidative and nitrosative stress, and increased activity of protein kinase C may also lead to neuropathy. Furthermore, the etiology of moderate to severe pain in few patients with diabetes and no pain at all in other patients with diabetes is not well understood. Diabetic neuropathy, if painful can adversely affect the quality of life often imposing limitations on the physical activities. Diabetic neuropathy is often unreported and untreated until it turns severe.[12]

Our study population is representative of Indian patients with type 2 diabetes, recruited uniformly across different zones, presenting with diabetic neuropathy, both painful and painless. This epidemiological study reports types of diabetic neuropathies with clinical presentation, associated co-morbidities, potential risk factors, and common treatment practices in type 2 diabetes and diabetic neuropathy in a large sample of patients.

The median duration of diabetic neuropathy is about 2 years, which demonstrates an early onset of diabetic neuropathy within 6 years of reported duration of type 2 diabetes in our study population. The prevalence of peripheral neuropathy in type 2 diabetes is 32.1%, which increases with age and duration of diabetes.[13] Almost half of the study patients had painful neuropathy. The nerve dysfunction and damage induced by hyperglycemic state leads to

hyperexcitable peripheral and central pathways of pain.[14] The prevalence of neuropathic pain in the diabetic population may be difficult to estimate as many patients do not report their symptoms until their pain is severe (29.2%) or burning sensation (28.0%) as the only presenting symptom or as combination of these symptoms. When blood glucose and blood pressure are excessively high, diabetes results in damage to nerves throughout the body. This damage can affect areas such as the extremities, such as hand or feet. Nerve damage in these areas can lead to pain, tingling, and loss of feeling.

Acute sensory neuropathy and chronic sensorimotor distal neuropathy are the two major types of neuropathies reported in our study which are also the most commonly occurring diabetic neuropathies.[15,16] Acute sensory neuropathy has acute or subacute onset of severe discomfort and is associated with hyperglycemia and may gradually lessen as euglycemia is reached. Chronic sensorimotor distal neuropathy is a long-term complication associated with symptomatic pain and other clinical signs of neuropathy. Patients with diabetes are at an increased risk to develop polyneuropathies as well, including chronic inflammatory demyelinating polyneuropathy and generalized symmetric polyneuropathy. Polyneuropathies are associated with extreme neuropathic pain, increased morbidity and impaired quality of life.[17] In this study, polyneuropathy also developed quite earlier in the disease course. Polyneuropathies are reported to develop and manifest within 10-15 years of diabetes duration; our diabetic cohort had reported polyneuropathies in about 16% of the total study population with median of 6 years of diabetes and 2 years of neuropathy onset.

Poor glycemic control, advanced age, hypertension, long duration of diabetes, dyslipidemia, smoking, heavy alcohol intake are the known potential risk factors associated with diabetic neuropathy.[18] Poor glycemic control and hypertension emerge as the most prevalent associated risk factors contributing to development of diabetic neuropathy. Though strong associations between smoking and diabetic microvascular complications; and between alcohol consumption and peripheral neuropathy is known,[19,20] the proportion of patients reporting these habits was quite low in this study.

Mean value of HbA1c more than 7% as observed in our study patients is an indicator of chronic hyperglycemia and poor glycemic control, responsible for alterations in cellular homeostasis, and diffuse vascular damage. The Indian data[**Error! Bookmark not defined.**] from the A1chieve study recorded baseline HbA1c value of 9.2 (± 1.4)% and the global[21] mean HbA1c was 9.5 (±1.8)%. Poor glycemic control is not just a problem in India but a global challenge considering the stringent requirement of controlling glucose levels to delay the progression of diabetic neuropathy as well as other complications. Prolonged exposure to high blood sugar causes nerve damage, resulting in different types of neuropathies. Additionally, majority of

our study population had uncontrolled levels of glucose. Poor glycemic control is a known risk factor associated with onset of neuropathy in diabetes patients. Furthermore, Al- Ani et al,[22] described co-existence of metabolic lipid disturbances with diabetic neuropathy irrespective of duration of disease. Abnormal levels of lipids induce oxidative stress in root ganglia sensory neurons, which may lead to diabetic neuropathy. Similar observations were made in this study wherein about two-third of patients had LDL-C levels greater than 100 mg/dL and triglycerides greater than 150 mg/dL.

Hypertension is a common accompaniment of type 2 diabetes, which has been reported in this study. Obesity, inflammation, oxidative stress, and insulin resistance are the common pathways which interact and form a vicious cycle. There is substantial overlap in etiology and disease mechanisms between hypertension and diabetes, which are the end results of metabolic syndrome. There is always a possibility of development of one after the other in the same individual.[23]Few of our study patients also had low levels of vitamin D. Vitamin D deficiency is associated with markers of impaired glucose metabolism, such as HbA1C and contributes to insulin resistance. Vitamin D receptors and vitamin D-binding proteins are present in pancreatic tissue and a relationship exists between certain allelic variations in genes for these two receptors with glucose tolerance and insulin secretion, which suggests an active role for vitamin D in the pathogenesis of T2DM. Also, vitamin D directly acts on pancreatic beta-cell function and regulates plasma calcium levels which affects insulin synthesis and secretion. Vitamin D replenishment improves glycemia and insulin secretion in patients with T2DM with established hypovitaminosis D.[24,25]

FPG and PPG contribute to approximately three-fourth and one-fourth of the mean glycemia, respectively. Hence, some practitioners believe in the axiom, 'fix the fasting first' with the recommendation to use metformin and sulfonylureas first because they each lower the FPG by 60-70 mg/dL, whereas thiazolidiones lower FPG by only 45-55 mg/dL.[26] Metformin followed by glimepiride were the two most commonly prescribed antidiabetic medications in our study population. In the absence of renal or hepatic dysfunction, metformin is the first line glucose lowering agent prescribed with lifestyle modification. In UK Prospective Diabetes Study (UKPDS), early intervention with metformin in patients with T2DM decreased the incidence of diabetes related vascular endpoints by 32%, myocardial infarction by 39%, diabetes related deaths by 42% and all-cause mortality by 36%.[27] However, metformin also decreases vitamin B12 levels due to possible alteration of small bowel motility stimulating bacterial overgrowth and competitive inhibition or inactivation of vitamin B12 absorption.[28]

Vitamin B12 deficiency has been documented to cause a distinct sensory polyneuropathy mimicking the symptoms of diabetic neuropathy. In diabetic patients with co-existing vitamin B12 deficiency, worsening of diabetic neuropathy was noted.[29] A cross sectional study identified 22% of type 2 diabetes patients with vitamin B12 deficiency.[30]Cobalamin deficiency was found in elderly diabetic individuals and was associated with neuropathy.[31]

Use of insulin can cause endoneurial ischaemia, hypoglycaemic microvascular neuronal damage and regeneration of nerve firing, which is a reversible disorder. Insulin neuritis is characterized by acute severe distal limb pain, peripheral nerve fibre damage and autonomic dysfunction, preceded by a period of rapid glycemic control.[32] Our study population had few patients (11%) prescribed with insulin and its derivatives and most of them presented with painful diabetic neuropathy. It is advisable, that patients prescribed with insulin are closely monitored and regularly screened to ensure early diagnosis of this variant of neuropathy, to avoid further complications.

In adult diabetic patients, 1500 mcg of methylcobalamin for 24 weeks decreased the occurrence of common symptoms of diabetic neuropathy such as tingling, weakness and pain.[33]A meta-analysis of 30 randomized clinical trials has shown that mecobalamin or methylcobalamin, a vitamin B12 complex, is effective and well tolerated in the treatment of diabetic neuropathy.[34] Methylcobalamin have the ability to donate methyl groups to the myelin sheath that insulates the axon; and for DNA metabolism which causes nerve regeneration.**Error! Bookmark not defined.**

Pregabalin is approved by the US Food and Drug Administration for painful diabetic neuropathy. It acts peripherally at the GABA receptor to block the perception of pain with rapid onset of sustained pain relief. The efficacy of pregabalin towards pain is due to its ability to bind to the auxiliary α2-δ subunit of the voltage-sensitive calcium channel, thereby decreasing Ca2+ influx at nerve terminals and modulating neurotransmitter release.[35]It is relatively well tolerated and causes less sedation than gabapentin. Various studies have already reported the beneficial effects of pregabalin in diabetic neuropathy.[36,37] Mecobalamin and pregabalin were the most frequently used medications in the treatment of painful and painless diabetic neuropathy. However, pregabalin was commonly prescribed in painful variant.

Diabetic neuropathy leads to substantial morbidity, discomfort and increased mortality according to its severity. Lack of awareness and inappropriate management increases morbidity eventually incurring substantial health care costs. Early diagnosis is important to allow immediate interventions, which decrease both mortality and morbidity. Also, patients

with diabetic neuropathy are at risk of insensate foot ulceration and must receive preventive education.

CONCLUSION

In summary, diabetic neuropathy represents a major health problem with significant morbidity due to painful neuropathy in almost half of the diabetic population. One-third of all diabetic patients reported acute sensory and chronic sensorimotor neuropathy. Onset of diabetic neuropathy could be much earlier than expected and hence, routine screening is recommended. This is one of the large-scale studies that shows poor glycemic control still remains an important risk factor in development of neuropathy. Other co-morbid conditions, especially hypertension further worsens the management of diabetes and diabetic neuropathy. Metformin and mecobalamin are the most common drugs prescribed for the treatment of diabetes and diabetic neuropathy respectively. Pregabalin is prescribed more for the treatment of painful diabetic neuropathy.

DISCLOSURE:

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